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June 3, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Docket No. 02D-0095

Dear Sirs:

Please find attached comments from Otsuka Maryland Research Institute (OMRI) on the Guidance for Industry - Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications.

Please feel free to contact me at (240) 386-3569 or contact Dr. Suresh Mallikaarjun at (240) 683-3221 should you need additional information.

Sincerely yours,

Suva B. Roy

Suva B. Roy, Ph.D.
Senior Director, Regulatory Affairs CMC

Enclosure: Attachment 1

02D-0095

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Attachment 1

Guidance for Industry
Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications

Comments

Page 2: Section II:

Line 66: "Exposure" should not refer to "dose". This is too vague and leads to confusion operationally as to what discipline is responsible for design, analysis, interpretation, and reporting. Not all of the "dose" may go into solution and not all of the "dose" may be systemically available. Experts in PK-PD should lead the team in this area.

Page 3: Section A:

Line 91: phase 1 and 2 studies that..... should read "phase 1 and 2 studies should attempt to...."

Line 93: effects) can also.... Should read "effects) in order to ...."

Overall Comment for Lines 88-101:

Well defined. Need to put this into practice routinely.

Page 4: Third paragraph in section 1

Line 158: In some cases,.... Should read "In several cases, ..."

Line 158-166: change the word "levels" to "concentrations"

Line 159: delete the word "can" and change the word "provide" to "provides"

Line 164: Change "Blood levels" to "Measurement of drug concentrations"

Lines 158-160: Weak. Needs to be beefed up to routinely look at Cp

Line 163: Even when there is a linear relationship, there can be high variability.
Pg: - P-gp CYP3A4

Page 7: Lines 284-286: Unclear what is meant by this?

Page 8: Section A

Line 332: Delete the work "can" and replace it with "may". Change the word "an" to "a" and delete the word "appropriate". After the words "starting dose" add "for the patient". Delete the sentence on line 333.

General comment for line 333-334

This cannot be done without knowing the exposure-response relationship.

Page 9: Section B
Line 367: change the word "*umbrella*" to "*bell*".

Line 369 "confounding of concentration and response". These are two independent variables—unclear how they could be confounded. The sentence is confusing and should be deleted.

Line 372: This is typically how exposure-response relationships are determined in the patient population. So it is not clear what the intent is in stating this.

Page 16: Line 618: after the word "formally," add "can"

Page 16: Line 619: "examine potential pharmacodynamic interactions". Not clear how this is linked?

Page 19: Section VII

Line 746: change "should follow the" to "may be based on the"

Line 747: delete "with special attention to" and replace with "modified to address"

General Comments for lines 746-752:

There are several limitations to writing a PK/PD report in a safety/efficacy format which is what the ICH guidance on clinical study reports is intended for.

Additional Comments:

The guidance states

This guidance describes (1) the uses of exposure-response studies in regulatory decision-making,
(2) the important considerations in exposure-response study designs to ensure valid information,
(3) the strategy for prospective planning and data analyses in the exposure-response modeling

process, (4) the integration of assessment of exposure-response relationships into all phases of
drug development, and (5) the format and content for reports of exposure-response studies.

I find that the organization of the document does not match these objectives.
1) is covered in Section III.

2) is covered in Section V.
3) is covered in Section VI.
5) is covered in Section VII.

I do not see how Section IV contributes to the above 5 statements.

I believe Item 4) is somewhat considered as part of Section III.

Background section uses the term "blood levels" instead of "blood concentrations". All other sections refer to the concentration-time curves.

Questioning the use of the term "well-established surrogate" when referring to QT interval:

Per FDA definition, a surrogate is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit"[1], or in this case, clinical harm/toxicity. Although lengthening of the QT interval is considered a risk factor for the occurrence of the clinical event in question (torsades de pointes), should it be considered a "well-established surrogate?" The predictive power of the QT interval is confounded by multiple factors (i.e. intra-individual variability, circadian rhythmicity/temporal variation, meal ingestion, physical activity, method of ECG assessment and correction, to name a few.) Drugs that prolong QT are not necessarily associated with torsades de pointes, and according to the Biomarkers Definition Working Group, use as a surrogate "requires demonstration of its accuracy (the correlation of the measure with the clinical endpoint) and precision (the reproducibility of the measure)."[2] With questionable predictive capability and no consensus regarding clinically relevant magnitudes of prolongation nor regarding the optimal method of correction, QT interval falls short of being considered "well-established."

[1] 21 CFR 314.510
[2] Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89-95.